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Title: Non-ischaemic cardiomyopathy, sudden death and implantable defibrillators. A review and meta-analysis.

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Abbreviations

AVID Antiarrhythmics versus Implantable Defibrillators

AMIOVIRT Amiodarone Versus Implantable Cardioverter-Defibrillator

CAT The Cardiomyopathy Trial

CIDS Canadian Implantable Defibrillator Study

COMPANION Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure

DANISH Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart

Failure on Mortality

DEFINITE Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation trial

SCD-HeFT Sudden Cardiac Death in Heart Failure Trial

ABSTRACT

Objective The recent Danish Study to Assess the Efficacy of ICDs [implantable cardioverter defibrillators] in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH) trial suggested that ICDs do not reduce overall mortality in patients with non-ischaemic cardiomyopathy (NICM), despite reducing sudden cardiac death. We performed an updated meta-analysis to examine the impact of ICD therapy on mortality in NICM patients.

Methods A systematic search for studies that examined the effect of ICDs on outcomes in NICM was performed. Our analysis compared patients randomised to an ICD with those randomised to no ICD, and examined the endpoint of overall mortality.

Results Six primary prevention trials and two secondary prevention trials were identified that met the pre-specified search criteria. Using a fixed-effects model, analysis of primary prevention trials revealed a reduction in overall mortality with ICD therapy (RR 0.76, 95% CI 0.65-0.91).

Conclusions Although our updated meta-analysis demonstrates a survival benefit of ICD therapy, the effect is substantively weakened by the inclusion of DANISH – which is both the largest and most recent of the analysed trials - indicating that the residual pooled benefit of ICDs may reflect the risk of sudden death in older trials which included patients treated sub-optimally by contemporary standards. As such, these data must be interpreted cautiously. The results of DANISH emphasise that there is no 'one size fits all' indication for primary prevention ICDs in NICM patients, and clinicians must consider age and comorbidity on an individual basis when determining whether a defibrillator is appropriate.

KEY QUESTIONS

What is already known about this subject?

Evidence for a mortality benefit with implantable cardiac defibrillators in patients with non-ischaemic cardiomyopathy has always been less robust than for patients with ischaemic cardiomyopathy, depending on a meta-analysis of trials which, individually, did not show a statistically significant benefit. The results of the recent DANISH trial suggested that ICDs may not reduce overall mortality in the modern era.

What does this study add?

Our meta-analysis and critical review provides an update in this field. Although a mortality benefit of defibrillators in NICM patients is still apparent in our pooled analysis, careful interpretation of these data suggest that the neutral result of DANISH may more accurately reflect the utility – or relative lack therein – of ICDs in the modern era. In part, this is because contemporary heart failure therapy reduces both sudden cardiac death and death from worsening heart failure, thus making an additional beneficial effect of defibrillator therapy on overall mortality harder to demonstrate. Closer analysis of DANISH suggests that younger patients with little co-morbidity may still benefit from an ICD, at least in the medium-term when their functional limitation is not severe.

How might this impact on clinical practice?

An individualised approach focusing on risk stratification according to patient age and comorbidity is required.

INTRODUCTION

The success of primary and secondary prevention implantable cardioverter defibrillators (ICDs) in reducing mortality in patients with coronary artery disease and left ventricular systolic dysfunction (LVSD) or heart failure with reduced ejection fraction (HFrEF) is well documented.[1,2,3] Concurrent trials seeking to validate the use of ICDs in patients with non-ischaemic cardiomyopathy (NICM) have been less successful. Pre-specified subgroup analyses of early secondary prevention ICD trials had suggested there was no significant difference in the benefit derived by patients with ischaemic cardiomyopathy (ICM) and NICM.[4,5] However, the first two primary prevention ICD trials to focus exclusively on NICM recruited only 207 patients between them before stopping early for futility.[6,7] Current guidelines for primary prevention ICDs in NICM are based largely on a meta-analysis of randomised controlled trials (RCTs).[8,9,10] In a combined analysis of five primary prevention trials, Desai *et al* reported a significant reduction in all-cause death in patients randomised to an ICD compared with medical therapy: RR 0.69; 95% CI, 0.55-0.87; p=0.002.[10] However, the validity of these findings in the contemporary era has been cast into doubt by the results of the recent Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH) trial, which found that ICDs did not reduce overall mortality.[11] We conducted an updated meta-analysis to examine the efficacy of primary prevention ICDs in NICM.

METHODS

Search strategy and study selection

We sought to determine the treatment effect of ICDs on all-cause death in NICM patients enrolled into primary (and, as a sub-analysis, secondary) prevention trials. We systematically identified published RCTs using computer-aided searches of Medline and Embase (from 1946 or 1947 respectively) to January 2017, using the terms "defibrillator" and "implantable" as search terms in the abstract, MeSH subject heading, keyword heading or title fields. Restrictions and eligibility

criteria are detailed in the supplementary appendix. Eligible studies were subcategorised into primary and secondary prevention trials, with only primary prevention trials selected for the primary meta-analysis, due to the assumption of highly heterogeneous baseline risk between these populations; secondary prevention trials were included in a secondary pooled analysis. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart detailing the selection process is presented in Figure 1.

FIGURE 1 HERE

Statistical analysis

We used summary statistics from the individual trials because patient-level data were not available for all studies. Hazard ratios (HRs) and 95% confidence intervals (CIs) regarding all-cause mortality in both ICD and control groups from original trial results papers were used as the principal summary measures where available. Single-study estimates were combined using inverse variance-weighted averages of logarithmic RRs in both fixed- and random-effects analysis. Heterogeneity between studies was assessed using the I^2 statistic. In the absence of significant heterogeneity the fixed-effect estimate was used. Pre-specified sensitivity analyses assessed the contribution of any single trial to the pooled estimate by recalculating the pooled RR after excluding single trials one by one. To determine the effect of follow-up duration in primary prevention trials, pooled estimates were recalculated separately for trials with a mean or median follow-up of less than three years, and three or more years. Publication bias was sought using a funnel plot [supplementary appendix Figure 1] and Eggers's test for small-study effects.

RESULTS

Eight randomised controlled trials were identified that met the pre-specified search criteria, of which six were primary prevention trials, and two were secondary prevention trials. The design and population characteristics of these trials are summarised in Table 1. We present a narrative overview of the primary prevention trials, followed by the results of our meta-analysis.

Overview of primary prevention ICD trials included in this meta-analysis

Pre-DANISH

As already discussed, the first two primary prevention ICD trials to focus exclusively on NICM were halted early due to futility.[6,7] In the Cardiomyopathy Trial (CAT) this was due at least in part to the unexpectedly low event rate, with interim analysis revealing a 1-year mortality rate of only 5.6% for all patients.[6]

The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial subsequently randomised 458 patients with NICM treated with standard medical therapy to an ICD for primary prevention purposes or no ICD.[12] Patients were predominantly in New York Heart Association (NYHA) functional class III and rates of angiotensin-converting enzyme (ACE) inhibitor and beta-blocker use were 86% and 85%, respectively (Table 1). Mineralocorticoid receptor antagonists (MRAs) were not recommended as standard therapy at that time, and rates of their use were not reported. Over a mean follow-up of 29 months there were only 68 deaths. Although there was a significant reduction in arrhythmic sudden death in the ICD group (HR 0.20, 95% CI 0.06 to 0.71; p=0.006), there was no difference in all-cause death (HR 0.65; 95% CI 0.40 to 1.06; P=0.08).[12] The rate of arrhythmic death was lower than anticipated, comprising only a third of all deaths in the standard-therapy arm.[12]

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) randomised 2521 patients with HFrEF to placebo, amiodarone or an ICD.[13] The majority of patients were in NYHA functional class II and almost half had NICM. The rate of prescription of an ACE inhibitor was similar to that in DEFINITE (83-87%), but beta-blocker use was lower (69%), and only 20% of patients were prescribed a MRA at baseline. Overall, ICD treatment reduced all-cause death by 23% (HR 0.77; 97.5% CI 0.62 to 0.96; P=0.007). The benefit of ICD therapy appeared to be greatest in patients in NYHA functional class II, consistent with other studies which have shown that patients with more advanced symptoms are more likely to die from pump failure.[14,15,16] Although patients with a non-ischaemic aetiology were at lower risk than those with an ischaemic aetiology, the reduction in all-cause death was similar in each subgroup: non-ischaemic HR 0.73 (95% CI 0.50-1.07) and ischaemic HR 0.79 (95% CI 0.60–1.04).

The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure trial (COMPANION) randomised 1520 heart failure patients in NYHA functional class III and IV to standard medical therapy alone or in conjunction with either a cardiac resynchronisation pacemaker (CRT-P) or cardiac resynchronisation defibrillator (CRT-D).[17] Both ICM and NICM patients were included. Among patients with non-ischaemic cardiomyopathy, CRT-D therapy led to a lower risk of all-cause death, as compared with pharmacological therapy (HR 0.50; 95% CI 0.29-0.88). In patients with ischemic cardiomyopathy, the HR was 0.73 (95% CI 0.52-1.04).

When considering the meta-analysis by Desai *et al*, it is important to note that, for the COMPANION trial, the treatment effect analysed was that between groups receiving CRT-D and pharmacotherapy, ignoring the CRT-P group.[10] Thus, in this analysis, assessment of the effect of ICD therapy was confounded by the coupled effect of CRT. However, the efficacy of ICD therapy remained statistically significant even if COMPANION was excluded, ie. even after removing all CRT-D

patients. Recently, a comparison of the effect of CRT-D with CRT-P (on top of medical therapy) from COMPANION trial was published [18]: the hazard ratio for all-cause death was 0.84 (0.65, 1.09); for cardiovascular death it was 0.73 (0.55, 0.98) and for sudden death 0.37 (0.21, 0.65). It is instructive to compare these findings with the DANISH trial, where the background use of CRT-P was frequent.

The DANISH trial

The DANISH trial enrolled 1116 patients with heart failure due to NICM, randomising them to conventional therapy (medical treatment and CRT-P if indicated) or an ICD added to conventional therapy.[11] Patients were almost exclusively in NYHA functional class II-III. After a median follow-up of 5.6 years, there was no reduction in the primary endpoint of all-cause death (251 deaths in total) for patients randomised to ICD therapy (HR 0.87; 95% CI 0.68-1.12; p=0.28). This was despite a significant reduction in sudden cardiac death in the ICD group (HR 0.50; 95% CI 0.31-0.82; p=0.005), although there was a total of only 70 patients with sudden cardiac death in the trial. The hazard ratio for cardiovascular death (172 deaths) was 0.77 (95% CI 0.57-1.05; p=0.10).

Rates of evidence-based medical therapy for heart failure were high in DANISH and more than half of patients (58%) received CRT, unlike those in previous ICD trials, with the exception of COMPANION. However, there was no evidence that background CRT explained the lack of benefit of ICD implantation. Specifically, in DANISH, the HR for the ICD group compared with the control group was 0.83 (95% CI 0.58−1.19) for individuals without CRT and 0.91 (95% CI 0.64−1.29) in those with CRT, with an interaction P-value of 0.73.

More relevant is the fact that both optimal medical therapy and CRT reduce the risk of each of sudden cardiac death and pump failure death and, therefore, cardiovascular death overall.[8,9] As a result, patients with an already relatively low absolute risk of sudden death because of their non-ischaemic (compared with ischaemic) aetiology, receiving excellent medical and device treatment, had little

room for further reduction in this mode of death (and for any reduction in sudden cardiac death to reduce cardiovascular death and, consequently, all-cause death). Illustrating this, the absolute rate of sudden cardiac death was low even in the control group (8.2% of patients in the control group suffered sudden cardiac death – less than 2% per year), as was sudden cardiac death as a proportion of cardiovascular death (48% in the control group). Furthermore, cardiovascular mortality comprised only 73% of all-cause death in the control group, which is relatively low compared to older heart failure trials [19]. This exemplifies the falling burden of sudden cardiac death and cardiovascular mortality in heart failure trials, attributable to modern treatment strategies, which are effective at reducing these causes of death [19].

Consequently, in a contemporary trial involving optimally-treated patients, such as was DANISH, even a large relative risk-reduction in sudden cardiac death will have a small impact on overall mortality if only a modest proportion of all deaths are cardiovascular and, in turn, only a moderate proportion of those are sudden. In addition, in patients with heart failure, there is the competing risk of non-sudden cardiovascular death, particularly death from worsening pump failure i.e. by preventing only one of the two common modes of death in heart failure, ICDs may effectively switch the mode of cardiovascular death, especially as severity of heart failure increases over time (this is how ICDs, notably, differ from drugs which reduce each of the two main modes of death in heart failure). Of course, when all-cause death is the primary endpoint, there is also the competing risk of non-cardiovascular death which is more common in older individuals with more co-morbidity and which increases proportionately during longer-term follow-up as non-cardiovascular co-morbidity develops with age. In this context, two findings of DANISH are notable. Firstly, there was a significant interaction between the effect of ICD treatment and age, whereby ICD treatment seemed to be of more benefit in younger compared with older patients: in patients <59 years HR 0.51 (0.29−0.92), in those aged ≥59 to <68 years HR 0.75 (0.48−1.16) and in those ≥68 years HR 1.19 (0.81−1.73). Secondly, there was a suggestion that the proportional-hazard assumption for all-cause

death was violated (i.e. when tested with Schoenfeld residuals, the P value was 0.054) and in keeping with this the Kaplan-Meier curves appeared to diverge during the initial 5 years of treatment where-after they converged. Overall, these findings can be interpreted as suggesting that ICDs reduce all-cause death in younger patients with little co-morbidity, at least in the short-term before the severity of heart failure increases with time (leading to a relatively higher risk of pump failure death) and co-morbidity develops (leading to a greater likelihood of non-cardiovascular death).

Results of meta-analysis

We did not include secondary prevention trials in our main meta-analysis. Pooled analysis of the six primary prevention trials (Figure 2), representing 2970 patients with NICM, demonstrated a 24% reduction in all-cause death with an ICD.

FIGURE 2 HERE

In a sensitivity analysis the benefit of ICD therapy was maintained after the removal of any single study from the pooled analysis. Neither did the exclusion of any single study, except DANISH, very substantively alter the magnitude of benefit from ICD therapy. If DANISH was excluded, the effect of ICD therapy was greater (RR 0.68; 95% CI 0.54–0.86, p=0.001). We performed a sensitivity analysis designed to test the effect of length of follow-up (average follow-up of each trial is listed in Table 1). Pooled analysis of primary prevention trials with less than 3 years follow-up showed a trend to greater benefit for ICD therapy (RR 0.61; 95% CI 0.43–0.86) compared to pooled analysis of trials with longer follow-up (RR 0.82; 95% CI 0.68–1.00) however the difference between these groups was not significant (P value for interaction = 0.13). The failure to reach statistical significance may be a result of having only three trials in either of these subgroups.

Pooled analysis of the six primary and two secondary prevention trials in combination (representing 3226 patients) also demonstrated a 24% reduction in all-cause death with ICD therapy (RR 0.76,

p=0.001). Variation in the pooled RR due to trial heterogeneity was not significant (I^2=0%; we therefore used a fixed-effects model although the estimate was identical in a random-effects model). We did not detect significant publication bias (supplementary appendix Figure 1).

We also examined the effects of defibrillator therapy on all-cause death when added to CRT (and medical therapy) in the two relevant primary prevention trials (COMPANION and DANISH). In total, these trials included 917 patients with CRT-D and 940 patients with CRT-P. There was a total of 364 deaths among these patients. Pooled analysis of these subgroups from COMPANION and DANISH did not demonstrate a benefit of CRT-D over CRT-P (Figure 3). It should be noted that ICM as well as NICM patients from COMPANION were included in this analysis, since outcomes for patients receiving CRT-D and CRT-P in COMPANION are not available broken down by aetiology. However, since ICM patients are no less likely to benefit from ICDs than NICM patients, their inclusion is unlikely to underestimate the benefit of defibrillator therapy.

FIGURE 3 HERE

DISCUSSION

What now for primary prevention ICDs in NICM? DANISH is the largest and most contemporary trial to address this issue, and its results are thought-provoking and potentially challenge current guidelines. Although our updated meta-analysis of primary prevention trials in NICM continues to show a significant survival benefit of ICD therapy, the inclusion of DANISH weakened this effect and the residual benefit may reflect the risk of sudden cardiac death in older trials which included patients treated sub-optimally by contemporary standards. In keeping with this, our meta-analysis of patients randomised to CRT-D versus CRT-P (on top of medical treatment) did not demonstrate a statistically significant survival advantage of defibrillator therapy in patients receiving CRT and pharmacological treatment. Nevertheless, our analysis does not completely exclude the possibility of a modest impact of an ICD on all-cause death, given the relatively small number of events and the wide confidence intervals around the point estimate for the treatment effect of defibrillator therapy (0.87, 0.72-1.05). However, even if there was a modest reduction in all-cause death with ICD treatment, it was obtained in patients who were not optimally medically treated. A beta-blocker was used in only 67% of patents in COMPANION, a rate of use which is low by contemporary standards.[20] In DANISH, MRA use was less than 60% and sacubitril-valsartan was not available. Both these therapies reduce sudden cardiac death and all-cause death.[8,21] The absolute benefit of an ICD is likely to diminish with further reductions in the absolute rate of cardiovascular death, and when the proportion of deaths due to cardiovascular causes is smaller, as will be the case in patients treated with better background medical and device therapy (i.e. CRT). In this scenario, even if they are effective, ICDs may not be cost-effective.

So which patients with NICM might obtain a worthwhile benefit from a primary prevention ICD? Subgroup analysis of DANISH suggested a reduction in all-cause death with ICD therapy in younger patients, as detailed above. The age subgroup analysis of DANISH suggested that the number of

premature deaths avoided per 100 patients treated for a median of 5 years was approximately 7.6 in those aged <59 years and 3.5 in individuals aged 59-to-67 years, giving numbers needed to treat (NNT) of 13 and 29, respectively. While at face value the absolute benefit in younger individuals looks clinically meaningful, accepting the potential for better background medical therapy, there is one other important consideration. ICDs are not without adverse effects. The delivery of inappropriate therapies has been reported in almost one-fifth of ICD recipients.[22] These constitute up to half of all shocks, despite advances in device programming [23] and are associated with an increase in mortality [23,24]. Other complications of ICD (or indeed CRT) implantation include lead fracture, device failure, and infection necessitating system extraction. The potential benefits of ICDs must always be weighed against these risks. Recent data from the USA show that older patients are at greater risk of complications after receiving an ICD.[25] These are also the patients less likely to benefit from an ICD. In DANISH, the rate of death from any cause among patients receiving an ICD in the age group <59, 59-to-67 and ≥68 was 10%, 21% and 31%, respectively. This implies that older patients die more frequently from causes that are not prevented by ICD therapy, such as pump failure and non-cardiovascular conditions. Since patients with heart failure in the real world are older and are afflicted by more comorbidities than those in clinical trials, these competing risks are likely to be more prevalent.

These new findings may help address the biggest challenge we have in using ICDs - identifying the minority of patients who have the optimum benefit/risk balance for a primary prevention ICD.

Clearly, the patients with NICM included in the existing trials are heterogeneous both in terms of aetiology and with respect to risk of sudden death. However, to date, the trials have provided little information about either type of subgroup. A vast array aetiological, functional, electrocardiographic, biomarker, and imaging variables have been evaluated in the quest to identify the patients who might have most to gain from an ICD. Although it is beyond the scope of this paper to analyse this

information, it is safe to say that no variable has yet proven sufficiently sensitive and specific for predicting SCD (as opposed to other modes of death). Currently, the most promising approach seems to be cardiac magnetic resonance imaging with late gadolinium enhancement to identify myocardial scar or fibrosis which is a substrate for ventricular re-entrant arrhythmias, although further prospective evaluation in NICM is required. The results of DANISH suggest that age and co-morbidity may be more valuable than these other investigations. The findings of DANISH also highlight the need to continually reassess the value of an ICD in each individual patient over time, with increasing age and the potential development of co-morbidity and worsening of heart failure symptoms (and the emergence of competing risks of non-cardiovascular death and death from worsening heart failure, respectively). The European Society of Cardiology 2016 heart failure guidelines, consistent with other guidelines, recommend an ICD in patients with NICM "to reduce the risk of sudden death and all-cause mortality in patients with symptomatic heart failure (NYHA class II–III), and a left ventricular ejection fraction $\leq 35\%$ despite ≥ 3 months of optimal medical therapy, provided they are expected to survive substantially longer than one year with good functional status (class I, level B)." It may be premature to suggest any change in the wording of the guidelines, especially as it is likely that further analyses of DANISH will be conducted and published which may help answer this question. However, the wording of the guidelines may not need any substantial change because the decision to implant an ICD will still be determined by functional status and life-expectancy, both of which are determined, in part, by age and co-morbidity. Indeed, the supporting text of current guidelines also states that "Patients with serious co-morbidities who are unlikely to survive substantially more than 1 year are unlikely to obtain substantial benefit from an ICD", which is consistent with the findings of DANISH. A suggested clinical approach to a patient being considered for an ICD is presented in Figure 4. The current guidelines also recognise that the appropriateness of an ICD may change over time and that the value of an ICD in an individual patient should always be re-assessed when generator replacement is needed. Deactivation of an ICD may

even be considered in certain circumstances e.g. in a patient receiving terminal care for heart failure or a non-cardiovascular illness. We believe that the findings of DANISH also support these recommendations.

INSERT FIGURE 4 HERE

Although DANISH was conducted in only one European country and the benefits and risks identified may not apply exactly to patients in other countries, the principles illustrated do relate more generally and should be individually applied to patients with NICM.

Table 1: Baseline patient characteristics in primary and secondary prevention ICD trials enrolling NICM patients

Characteristic	Secondary prevention trials		Primary prevention trials					
	AVID	CIDS	CAT	AMIOVIRT	DEFINITE	COMPANION	SCD-HeFT	DANISH
Year of publication	1997	2000	2002	2003	2004	2004	2005	2016
No. randomised	1016	659	104	103	458	(CRT-D vs CMT) 903	(ICD vs placebo) 1676	1116
No. (%) with NICM	193 (19.0)	63 (9.6)	104 (100)	103 (100)	458 (100)	397 (44.0)	792 (47.3)	1116 (100)
Follow-up, mean (SD), mo	18.2 (12.2)	35	66 (26.4)	24 (14.4)	29 (14)	Range 14.8 - 16.0	45.5	67.6 (NR)
Demographics								
Age, mean (SD), y	65 (10.5)	64 (9.6)	52 (11)	59 (11.5)	58	67	60	64*
Male, % (No.)	80 (808)	84.5 (557)	80 (83)	70 (72)	71 (326)	68 (611)	77 (1294)	72 (809)
NYHA class III/IV, % (No.)	9.5 (97)	10.8 (71)	34.6 (36)	20 (20)	21 (96)	100 (903)	31 (516)	47 (519)
Duration of CHF, mean	NR	NR	3 mo	3.2 y	2.8 y	3.5 y	24.5 mo	19 (NR)*
LVEF, mean (SD), %	31 (13)	34 (14)	24 (7)	23 (9)	21 (14)	22	25	25 (NR)*
Medications at baseline, % (No.)								
Ace inhibitor / ARB	68.5 (680)	NR	96.2 (100)	85 (88)	96.7 (443)	90 (810)	96 (1610)	97 (1077)
Beta-blocker	29.4 (292)	27.4 (181)	3.8 (4)	51.5 (53)	84.9 (389)	67 (608)	69 (1157)	92 (1026)
MRA	NR	NR	NR	19.4 (20)	NR	55 (496)	20 (333)	58 (646)
CRT	0	0	0	0	4.8 (11) in ICD group; NR in controls	66 (595) in treatment group	NR	58 (645)
Design	ICD vs antiarrhythmic	ICD vs amio.	ICD vs CMT	ICD vs amio.	ICD vs CMT	CRT-D vs CRT-P vs CMT	ICD vs amio. vs placebo	ICD vs CMT
Primary endpoint	ACM	ACM	ACM	ACM	ACM	ACM / ACH	ACM	ACM
Control 1-yr mortality, % (No./total)	18 (90/509)	11 (37/331)	4 (2/54)	10 (5/52)	6 (14/229)	19 (59/308)	NR	4 (20/560)
ICD (Transvenous/Epicardial), %	93 / 5	84 / 10	100 / 0	100 / 0	100 / 0	100 / 0	100 / 0	100 / 0
Internal validity								
Follow-up, %	100	100	100	100	100	>95%	100	100
Crossovers to ICD, % (No.)	18.9 (96)†	15.7 (52)	NR	15.4 (8)	10 (23)	26 (80)††	NR	4.8 (27)
Crossovers to control % (No.)	25.7 (130)	28.1 (92)	NR	21.6 (11)	1.7 (4)	NR	NR	7.9 (44)
Intention-to-treat	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes
Events committee	NR	Not blinded	NR	Blinded	Blinded	Blinded	Blinded	Blinded

Abbreviations: ACE, angiotensin-converting enzyme; ACH, all-cause hospitalisation; ACM, all-cause mortality; Amio., amiodarone; ARB, angiotensin-receptor blocker; CHF, congestive heart failure; CMT, conventional medical therapy; CRT-D, cardiac resynchronisation therapy defibrillator; CRT-P, cardiac resynchronisation therapy pacemaker; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NICM, non-ischaemic cardiomyopathy; NR, not reported; NYHA, New York Heart Association.

* Calculated as mean of stated medians for treatment and control groups

† For AVID, crossover rates are reported at 2 years

†† For COMPANION, rate of withdrawal from medical therapy group is reported as crossover rate

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Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

Identification

Records identified through Embase and Medline databases
(n = 1261)

Screening

Records after duplicates removed
(n = 891)

Records screened
(n = 891)

Records excluded
(n = 861)
Subgroup analysis = 232
Not an RCT = 283
Not ICD vs control = 333
Post-MI study = 11
Paediatric study = 2

Eligibility

Full-text articles assessed for eligibility
(n = 30)

Full-text articles excluded, with reasons
(n = 22)
Subgroup analysis = 1
Not an RCT = 7
Not ICD vs control = 4
No NICM patients = 4
Duplication = 4
Predominantly epicardial ICDs = 1
Trial population exclusively patients awaiting transplant = 1

Included

Studies included in qualitative synthesis
(n = 8)

Studies included in quantitative synthesis (meta-analysis)
(n = 8)

Primary prevention trials
(n = 6)
Included in main analysis

Secondary prevention trials
(n = 2)
Included in secondary analysis

Study	Years of enrollment	No. of Patients	Risk Ratio (95% CI)		
				Favours defibrillator	Favours no defibrillator
CAT	1991-1997	104	0.83 (0.45 - 1.52)		
AMIOVIRT	1996-2000	103	0.87 (0.32 – 2.42)		
DEFINITE	1998-2002	458	0.65 (0.40 – 1.06)		Heterogeneity I^2 = 0%
SCD-HeFT	1997-2001	792	0.73 (0.50 – 1.07)		
COMPANION	2000-2002	397	0.50 (0.29, 0.88)		
DANISH	2008-2014	1116	0.87 (0.68 – 1.12)		
Combined		2970	0.76 (0.65 – 0.91)	p = 0.002	

Risk Ratio (95% CI)

Size of the data marker corresponds to the relative weight assigned in the pooled analysis using fixed-effects models

Figure 3: All-Cause Mortality Among Patients Randomised to CRT-D or CRT-P in Primary Prevention Trials

Study	Year of enrollment	No. of Patients	Risk Ratio (95% CI)		
				Favours CRT-D	Favours CRT-P
				Heterogeneity $I^2 = 0\%$	
COMPANION	2000-2002	1212	0.83 (0.66 – 1.05)		
DANISH	2008-2014	645	0.94 (0.69 – 1.29)		
Combined		**1857**	**0.87 (0.72 – 1.05)**	**p = 0.138**	

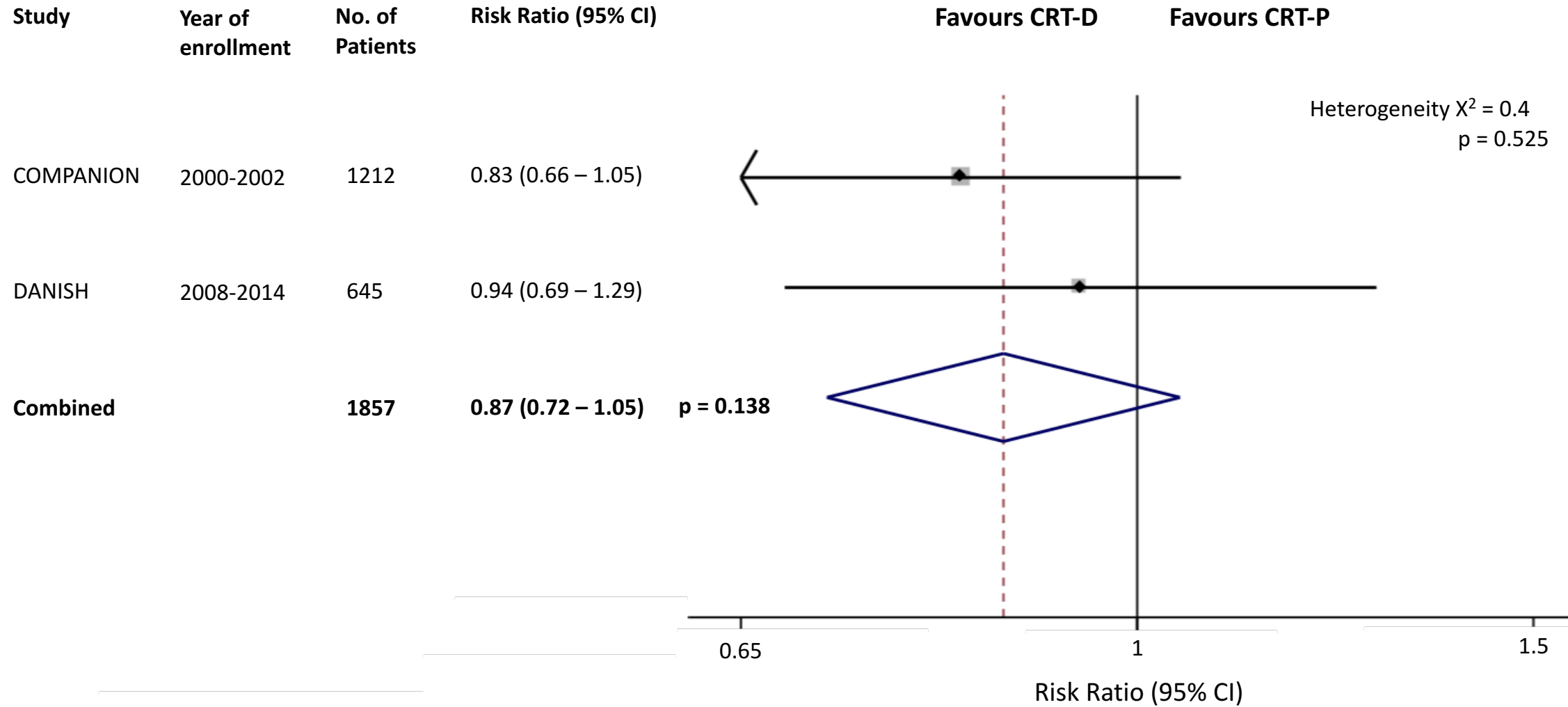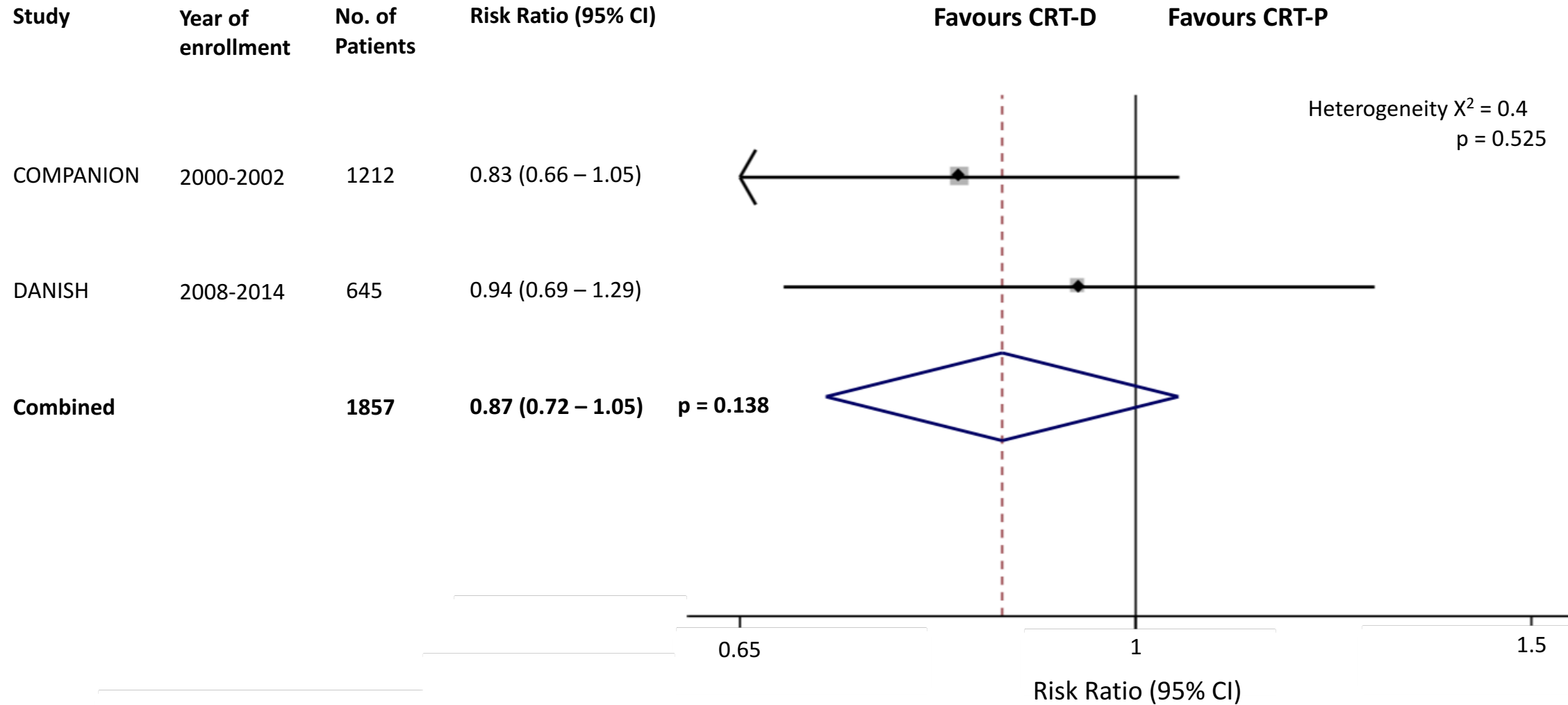0.65   1   1.5

Risk Ratio (95% CI)

Size of the data marker corresponds to the relative weight assigned in the pooled analysis using fixed-effects models

Figure 3: All-Cause Mortality Among Patients Randomised to CRT-D or CRT-P in Primary Prevention Trials

Study	Year of enrollment	No. of Patients	Risk Ratio (95% CI)		
					Heterogeneity X^2 = 0.4
					p = 0.525
COMPANION	2000-2002	1212	0.83 (0.66 – 1.05)		
DANISH	2008-2014	645	0.94 (0.69 – 1.29)		
Combined		**1857**	**0.87 (0.72 – 1.05)**	**p = 0.138**	

Favours CRT-D   Favours CRT-P

0.65   1   1.5

Risk Ratio (95% CI)

Size of the data marker corresponds to the relative weight assigned in the pooled analysis using random-effects models

Figure 2: All-Cause Mortality Among Patients Randomised to CRT-D or CRT-P in Primary Prevention Trials

Study	Year of enrollment	No. of Patients	Risk Ratio (95% CI)
COMPANION	2000-2002	1212	0.83 (0.66 – 1.05)
DANISH	2008-2014	645	0.94 (0.69 – 1.29)
Combined		1857	0.87 (0.72 – 1.05) p = 0.138

Heterogeneity X^2 = 0.4
p = 0.525

Favours CRT-D   Favours CRT-P

0.65   1   1.5
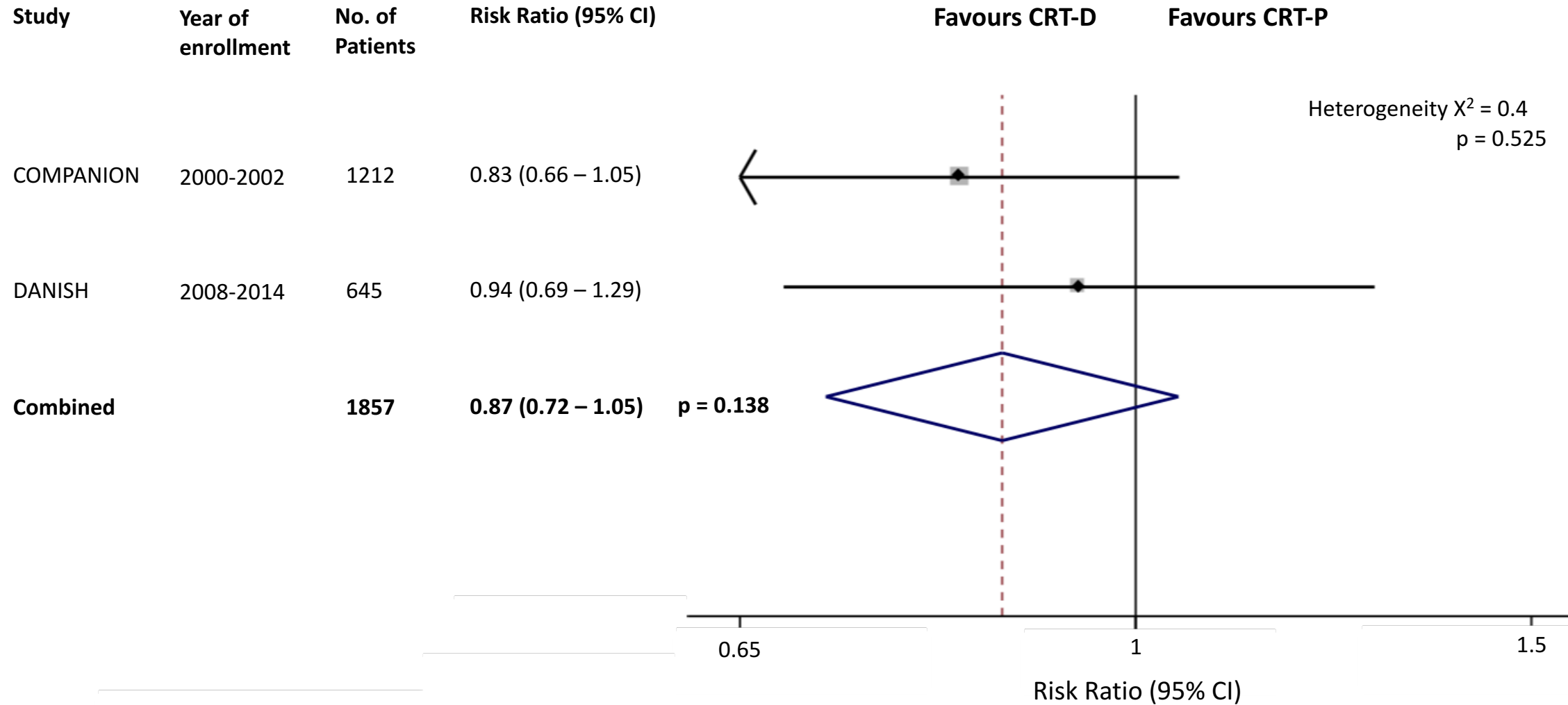
Risk Ratio (95% CI)

Size of the data marker corresponds to the relative weight assigned in the pooled analysis using random-effects models

Figure 4: All-Cause Mortality Among Patients Randomised to CRT-D or CRT-P in Primary Prevention Trials

Study	Year of enrollment	No. of Patients	Risk Ratio (95% CI)		
				Favours CRT-D	Favours CRT-P
					Heterogeneity $X^2 = 0.4$ p = 0.525
COMPANION	2000-2002	1212	0.83 (0.66 – 1.05)		
DANISH	2008-2014	645	0.94 (0.69 – 1.29)		
Combined		**1857**	**0.87 (0.72 – 1.05)**	**p = 0.138**	

0.65   1   1.5

Risk Ratio (95% CI)

Size of the data marker corresponds to the relative weight assigned in the pooled analysis using random-effects models

Figure 4: Suggested approach to consideration of an ICD in a patient with NICM
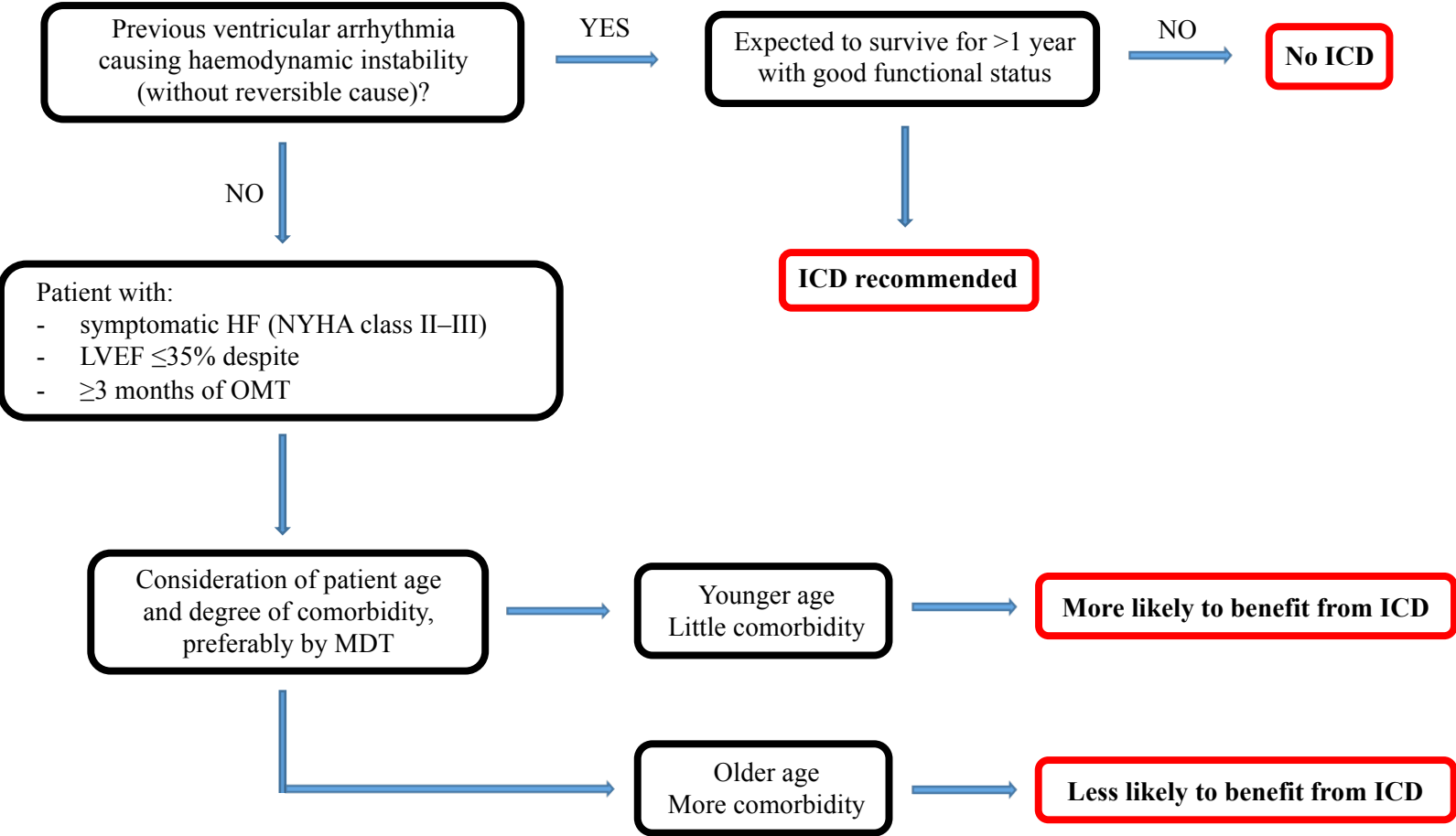
Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. ICD, implantable cardioverter defibrillator; MI, myocardial infarction; NICM, non-ischaemic cardiomyopathy; RCT, randomised controlled trial.

Figure 2 All cause mortality among patients with non-ischaemic cardiomyopathy randomised to implantable cardioverter defibrillator (ICD) or cardiac resynchronisation therapy defibrillator (CRT-D) versus medical therapy or medical therapy plus cardiac resynchronisation pacemaker (CRT-P) in primary prevention trials.

Figure 3 All-cause mortality among patients randomised to cardiac resynchronisation therapy defibrillator (CRT-D) or cardiac resynchronisation therapy pacemaker (CRT-P) in primary prevention trials.

Figure 4 Suggested approach to consideration of an implantable cardioverter defibrillator (ICD) in a patient with non-ischaemic cardiomyopathy. HF, heart failure; LVEF, left ventricular ejection fraction; MDT, multi-disciplinary team; NYHA, New York Heart Association; OMT, optimal medical therapy

SUPPLEMENTARY APPENDIX: Methods for study selection, data synthesis and statistical analysis

We sought to determine the treatment effect of ICDs on all-cause death in NICM patients enrolled into primary (and, as a sub-analysis, secondary) prevention trials. Our overall search strategy is presented in the main manuscript. Restrictions were imposed to limit the search to randomised controlled trials (RCTs) enrolling human subjects that were reported in English. To be eligible for inclusion in our meta-analysis, trial populations had to include patients with non-ischaemic cardiomyopathy. Trials that only enrolled patients awaiting heart transplantation were excluded. Trials had to include randomisation to an implantable cardiac defibrillator (ICD) or to a non-ICD control group. The majority of these ICDs were required to be transvenous systems, with epicardial systems deemed *a priori* to be a qualitatively different intervention. Trials in which mortality was a primary or composite outcome of the comparison of ICDs versus the control group were included. Trial titles and abstracts were initially screened, with potentially eligible trials subsequently undergoing more detailed analysis of the primary results paper. The risk of bias of individual studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias in RCTs. All trials were deemed either of low or unclear risk, with none deemed high risk; bias across studies was deemed unclear. Our analysis was not stratified further according to potential bias. This approach was agreed by all authors; no protocol is available.

Where HRs were not stated, risk ratios (RRs) and 95% CIs were generated using available data. Data were cross-checked against those used by Desai et al.[16] Data sought are presented in Table 1 of the main manuscript, with the exception of HR/RRs and 95%CIs, which are presented for individual trials in Figures 2 and 3 of the main manuscript.

APPENDIX FIGURE 1 HERE

This analysis has two limitations at review level. First, it was conducted using trial-level data rather than gold-standard, patient-level data, which were unavailable. Second, data for the COMPANION trial compared the treatment effect across CRT-D and pharmacotherapy groups, rather than comparing CRT-D and CRT-P groups. The potentially confounding effect of this is made clear in the main text of the manuscript. All analyses were conducted using STATA version 14.0 (StataCorp, College Station, TX). This work was not funded and there was no role of any funding source in the conception, data synthesis, analysis, interpretation, or in drafting of the manuscript.

Funnel plot to assess publication bias among trials utilised for meta-analysis